NTP Study Nomination:
4,7,10-Trioxatridecane-1,13-diamine [CAS RN 4246-51-9]

Background

4,7,10-Trioxatridecane-1,13-diamine (TTD) was nominated by the National Cancer Institute for toxicological testing—specifically, *in vitro* alternative test assays regarding potential acute toxicity and genotoxicity—based on its high production volume (>500 million to 1 billion pounds in 1998 and <1 million pounds in 2002 according to the U.S. EPA's Inventory Update Rule), potential exposure to workers, and limited toxicity data (http://ntp.niehs.nih.gov/go/32744). TTD is used in the production of polycondensation and polyaddition products, copolymers, emulsifying agents, corrosion inhibitors, and textile, leather, and paper auxiliaries. It is also used as a hardener and cross-linking agent for epoxy resins. Numerous patents for TTD can be found, which include its use in the preparation of impact- and abrasion-resistant coatings and in products that are impermeable to fluid but not air such as tents, footwear, disposable diapers, and feminine napkins. Occupational exposure to TTD is the most likely source of human exposure. According to the NIOSH National Occupational Exposure Survey (1981-1983), an estimated 13,486 workers (3,955 females) were potentially exposed in the workplace to TTD. Workers included aircraft engine mechanics, electrical and electronic equipment assemblers, janitors and cleaners, and painting and paint spraying machine operators; however, studies of human exposure to TTD specifically were not found. The rat oral LD_{50} is 4.29 mL/kg and the rabbit dermal LD_{50} is 2.50 mL/kg. TTD was a severe skin irritant in rabbits, producing severe erythema and moderate edema in all tested animals, ecchymosis and necrosis, scabs, and desquamation. Information provided by suppliers of TTD indicated that inhalation of TTD can cause spasms, inflammation and edema of the larynx and bronchi, pneumonitis, and pulmonary edema, but no studies were found to confirm this. Data from studies of subchronic or chronic toxicity, carcinogenicity, genotoxicity, or reproductive/developmental effects were not available nor were studies of TTD metabolism. The software program METEOR predicted several metabolites could be formed via oxidative deamination and oxidative *O*-dealkylation. In addition, TOPKAT and DEREK, software for assessing structure activity relationships, were used to predict toxicity. TOPKAT predicted TDD to be a carcinogen in male rats and female mice, but DEREK was unable to assess the toxicity.

Study Recommendations

TTD is recommended for *in vitro* biomolecular screening studies and genotoxicity studies. Information that could be gleaned from ICCVAM recommended assays (e.g. corrosivity, ocular toxicity, acute toxicity) is of limited utility for hazard identification given the existing database for TTD. TTD may, however, be useful as a reference compound for evaluating the performance of currently validated or future alternative test methods.